

From the Medical Policlinic of the University of Zürich
(Director: Prof. Dr. R. Hegglin)

Under the supervision of Dr. G. R. Constan

Evaluation of the Tolbutamide Response Test in the
Diagnosis of Diabetes Mellitus

Inaugural Thesis
to acquire the title of doctorate of the medical faculty of
the University of Zürich

presented by
Jean-Pierre Habicht
from Geneva and Schaffhausen

Accepted upon the recommendation of: Prof. Dr. R. Hegglin

Zürich 1963



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Introduction

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The recognition of diabetes mellitus is easy in the presence of typical subjective cardinal symptoms, fasting hyperglycaemia and glycosuria. In its early stages though, subjective complaints are lacking, fasting blood sugar concentration may be normal, and glycosuria absent or intermittent only (11, 12, 130).

To clarify such cases glucose tolerance tests are used (13, 26, 27, 28, 37, 40, 41, 42, 49, 58, 64, 75, 85, 86, 87, 88, 105, 113, 117, 118, 129, 131, 133). Unfortunately the form of the resultant blood sugar curve is not dependent upon insulin alone. Other hormones (67, 68, 78, 98), age (21, 104, 111, 112), certain stress situations (103) such as infections (8, 80, 92, 94, 108) and nervous strain, prolonged physical inactivity (10, 14), length of fasting period and general state of nutrition (24, 26, 31, 133, 134) also influence amongst other factors (3, 16, 29, 30, 55, 66, 69, 74, 79, 87, 90, 91, 95, 109, 114, 115, 116, 132) the course of the blood sugar curve. When ingested orally the amount, concentration and temperature of the glucose solution (5, 26) as well as the rate of its absorption (1, 12, 57, 60, 77, 110) also affect the outcome. So do the speed of injection and the pain of the needle prick when the glucose is administered intravenously (22, 26).

Because so many factors are involved it is understandable that amongst 678 patients with questionable diabetes, which were tested over the past two years with Constatm's (14, 28) modification of the Staub-Traugott oral glucose tolerance test, 229 showed normal, 171 pathological curves, whilst 278 cases could not be classified by the blood sugar curves alone.

The sensitivity of these glucose tolerance tests can be increased by ACTH or by glucocorticoids (7, 43, 44, 124, 125) but in regard to the specificity the above mentioned causes of uncertainty remain. These methods are moreover time consuming and cumbersome.

The elegant measure of glucose assimilation proposed by Conard (22, 50, 65) is unfortunately also burdensome. Searching for a better and, if possible, simpler procedure we came upon the intravenous tolbutamide response test as developed by Unger and Madison (119, 120, 121, 122) and the purpose of this study is to investigate its reliability and practicability.

In 1956 Mirsky, Diengott and Dolger (39, 83, 84) reported a different hypoglycaemic effect for healthy subjects than for diabetics after acutely administered tolbutamide. This difference was more consistent when the sulfonylurea was injected intravenously (15, 51, 62, 73, 82) and Pfeffer, Fuchs, Michel and Foerder (97) suggested that this might prove the basis of a diagnostic test for mild diabetes. The result of a few such attempts have been published (6, 38, 47, 70, 71, 72, 93, 99, 100, 101, 102, 106, 119, 120, 121, 122, 126, 137). See tables 1 and 2.

From experimental studies it seems that tolbutamide acts as an "insulin liberator" (4, 9, 18, 20, 23, 25, 32, 46, 48, 52, 53, 54, 61, 76, 98, 127, 128, 135, 136). Therefore the tolbutamide response test might be regarded as a measure of the insulin reserve in the pancreas.

Material and Method of Investigation

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Among the diabetics were those whose clinical symptoms, fasting blood sugar and/or reaction to a normal breakfast were pathognomic of their disease. To avoid burdening their precarious sugar metabolism these were spared a glucose tolerance test. All others had a diabetic reaction to this test besides clinical symptoms.

None of the controls suffered from any acute or chronic disease of consequence.

A third group of two cases only had liver disease, but a normal glucose tolerance test.

Method:

We tried to follow Unger and Madison's method (121) as closely as possible. It was impossible to control the preparatory diet of the out-patients. They were simply told to eat "well" the evening before, 14 hours before the test. They presumably all had a diet of at least 300 gms of carbohydrates per day (6, 76).

Between 8:00 and 9:30 a.m. after an overnight fast four duplicate capillary blood samples were taken and analysed according to the Somogyi Nelson (89, 107), or the Mendel Hoogland (81) methods.

One gram of sodium tolbutamide (Artosin*) in a 10% alkaline solution was injected intravenously within exactly two minutes. Further duplicate blood samples were obtained at 20, 30, 40 and 60 minutes after the midpoint of the injection.

Results:

In table 3 are the tolbutamide response values in mg % blood-sugar concentration of 26 diabetic patients and of 28 non-diabetic controls. The latter are divided up according to the

* We wish to express our gratitude to Professor J. D. Achelis of C. F. Boehringer & Soehne GmbH., Mannheim, Germany, for providing us with the Artosin solution.

time of their minimum blood sugar concentration (time of nadir); the subgroup N_{30} with their time of nadir at 30 minutes after the injection, and the subgroup N_{40} with the time of nadir at 40 minutes.

The diabetic patients, control subjects with nadir at 30 minutes, and control subjects with nadir at 40 minutes all show significant differences from each other ($P < 0.005$) at 30 minutes after the injection. Their mutual relationships have always been calculated separately (table 4).

The mean blood sugar response values of the diabetic group and of the whole control group expressed in percent fasting blood sugar agree well with those found by others (table 1). (6, 15, 73, 82, 97, 121, 137).

As can be seen in figure 1, the blood sugar concentration averages of the control group show a rapid decline, which reaches its minimum, as expressed in our samplings, at 30 or 40 minutes. The sixty minute values were always higher than these minimums. The diabetic response on the other hand is slower, the minimum is usually not attained within the hour of the test, and when it is, there is either no or only an insignificant rebound.

Side Reactions:

As others have reported (39, 73, 82, 83, 84, 93, 119, 120, 121, 122, 137) there is an occasional transitory burning sensation in the shoulder.

Among the non-diabetics, four subjects complained of moderate hypoglycaemic symptoms with sweating and nervousness. These subjective symptoms usually appeared five to ten minutes after the blood sugar concentration had fallen to its lowest point, and when it was already well on the rise again. In one of the first such cases we interrupted the test by oral glucose administration omitting this person from our study. The symptoms passed just as quickly for the three others without this measure. No other side effects were observed.

Discussion

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The best criterion for the diagnosis of diabetes mellitus must include within its limits the greatest proportion of diabetics (sensitivity), while excluding the greatest proportion of non-diabetics (specificity) (132). To this end we reviewed our data obtained by the tolbutamide response test and submitted it to statistical analysis (table 4).

The twenty and thirty minute values of the non-diabetics expressed in percent of the fasting blood sugar seem without correlation to the initial fasting blood sugar concentration ($P_r > 0.10$). There is, however, a very strong such correlation for the diabetics ($P_r < 0.001$). This is graphically demonstrated in figures 2, 2*, 3 and 3*. Figures 2* and 3* show that the more the average of the fasting blood sugar concentrations of the diabetic group approaches normality, the more the twenty and thirty minute response values move toward those of non-diabetics. The scattering of the diabetic individuals around these averages then causes a considerable overlap with the non-diabetics. This overlap is especially marked for those mild diabetics with normal fasting blood sugar; i.e. the patients who present a diagnostic problem. For this very reason the criterion of those authors who use the twenty and thirty minute tolbutamide response values expressed in percent of the initial fasting blood sugar concentration (6, 72, 100, 106, 121, 126) have shown such a low sensitivity (25, 36, 45, 48, 59, 93). For example, five of the sixteen diabetics in our material, whose fasting blood sugar concentrations were below 100 mg percent, i.e. within the normal range, would have failed to be diagnosed with Unger & Madison's criteria. Our observation is another illustration that using the percent of the fasting blood sugar values (2,35) in the investigation of carbohydrate metabolism may be inaccurate, as has been pointed out by Hemmingsen & Marks (63).

The absolute fall in blood sugar concentration (mg. percent) in twenty and in thirty minutes shows a significant difference between diabetics and non-diabetic subgroups ($P < 0.05$). The scattering of the individuals, however, still produces too great an overlap between the diabetic group and the non-diabetic subgroups, so that this criterion is also not reliable for the diagnosis of diabetes mellitus (figures 2 & 3).

According to table 4 the time and amount of rebound from the lowest tolbutamide response blood sugar value, e.g. nadir, seems a more useful criterion. This possibility has also been suggested by Zarowitz & Eis (137). Indeed in our small number of cases it proved to be without bias as to the initial fasting blood sugar values and to follow a "normal" distribution, when it was expressed in percent of the initial fasting blood sugar (%FBS). For these two reasons, the absence of bias and the "normal" distribution, it seems to us legitimate in this case to use the %FBS and we have tentatively chosen the criteria in table 5 until a larger sample is on hand to test our assumptions. The non-diabetics' blood sugar concentrations reach a minimum to rise again within the hour. However, some non-diabetics reach this minimum earlier, at 30 minutes (subgroup N_{30}), and some only at 40 minutes (subgroup N_{40}). Therefore the differentiation between the diabetics and the non-diabetics is undertaken separately for each of these non-diabetic subgroups. The criterion of differentiation between the diabetics and the non-diabetics of subgroup N_{30} (nadir at 30 minutes) is the 60 minute %FBS value minus the 30 minute %FBS value (table 5 A). For each value of this difference, found in the middle column, there corresponds a sensitivity (i.e. the proportion of diabetics included up to this value) and a specificity (i.e. the proportion of non-diabetics, subgroup N_{30} , excluded up to this value). For the differentiation between diabetics and non-diabetics of subgroup N_{40} (nadir at 40 minutes) the difference between the 60 minute N_{40} %FBS values and the 40 minute %FBS values must be used (table 5 B). From this table (table 5), we have chosen temporarily the following diagnostic criteria:

An individual is considered diabetic if his blood sugar reaches no minimum before 40 minutes and the difference between the 60 and 40 minute values is less than +3.5%FBS. The individual is considered non-diabetic if the difference between the 60 and 30 minute values is greater than +3.6%FBS or between the 60 and 40 minute values is more than +5.6%FBS.

In our small group these criteria provided an excellent differentiation between diabetic and non-diabetic (figures 4 & 5). Granted a "normal" distribution for the whole population, only about 2.5% of the individuals examined will fall between the limits (table 5), and will thus remain unclassifiable by means of this test. This would compare favourably with the glucose tolerance tests as mentioned in the introduction. Observation on a much larger group will be necessary to decide whether the absolute blood sugar values in mg percent can be used alone instead of the %FBS.

A review of the literature on the tolbutamide response test, with our criteria in mind have, however, suggested the following:

Late pregnancy (18,20) and extreme obesity (19, 123) sometimes produce a diabetic tolbutamide response. This is true, however, regardless of the criteria used.

Insulomas, using Unger & Madison's criteria, are easily differentiated from diabetes (33, 48). They have no rebound from their hypoglycemic nadir within the hour and would be falsely diagnosed as diabetic with our criteria.

In liver disease Fajans et al. (48) and Kaplan (71, 72) report tolbutamide response averages without or with only a minimal rebound within the first hour, which would agree with Kaup (1957) (73), who, however, used 2 gm of tolbutamide intravenously. Using 1 gm tolbutamide only Creuzfeldt & Kaup (1961) observed the rebound as one finds in non-diabetics (33).

In one patient with cirrhosis and another with chronic hepatitis, both showing normal glucose tolerance curves, we found no rise of the blood sugar before 60 minutes (table 6). Also when we apply Unger & Madison's criteria (121) to these two cases they would be diagnosed as diabetes. Longer observation only will decide whether an insular insufficiency was present.

Table 7 shows the influence of the fasting blood sugar concentration, sex and age on the time of the minimal blood sugar concentration in non-diabetics. The exact procedure of the χ^2 test was used (34) because the distribution was skewed. Only age has a marked effect on the time of nadir (36, 59, 72, 123). The younger non-diabetics usually have their nadir at thirty minutes, the older at 40 minutes.

Summary and Conclusion

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An intravenous tolbutamide response test was performed on 26 mild diabetics, 28 non-diabetic controls and 2 non-diabetic patients with liver disease. The results agree with those of the literature.

The influence of age, sex and fasting blood sugar were analysed. Generally younger non-diabetics reach their lowest blood sugar values earlier than older people. The initial fasting blood sugar concentration (FBS) of mild diabetics determines in great part the twenty and thirty minute values, when expressed in percent of FBS. These values in diabetics with normal blood sugar concentrations are too similar to those of non-diabetics to be useful as a diagnostic criterion.

The best criteria for differentiation between mild diabetics and non-diabetics are discussed; it is concluded that the form of the blood curve within the hour after the injection is the most reliable one. In non-diabetics the blood sugar curve falls and rises again within one hour. In diabetes with high fasting blood sugar, tolbutamide may have no or only an insignificant influence on the blood sugar. In diabetes with normal, or almost normal fasting blood sugar, tolbutamide lowers the glycemia, which reaches its minimum at forty minutes or thereafter. There is no or only an insignificant rise of the blood sugar within sixty minutes. From our small number of observations statistical analysis permits the temporary adoption of the following criteria:

	<u>60 minus 30 minute</u>	<u>60 minus 40 minute</u>
	<u>blood sugar values in %FBS</u>	
Non-diabetic	+3.6 or more	+5.6 or more
Diabetic	0.0 or less	+3.5 or less

It is possible that in severe liver disease the tolbutamide response curve may mimic mild diabetes. Our criteria cannot be used to differentiate between insulomas and diabetes. However according to the literature, in organic hyperinsulism the drop of the blood sugar in response to tolbutamide is greater than in non-diabetics.

Disadvantages of the tolbutamide response test are the need for an intravenous injection, and the occasional discomfort of hypoglycemia in normal subjects, which counsils prudence in its use on dehydrated patients, or subjects with insulomas or low adrenal or pituitary function, or those under the influence of ganglioplegic agents.

The advantages of a tolbutamide response test are that it does not damage the diabetic's precarious glucose tolerance, that it requires not more than four blood samplings, and that it lasts an hour only. Using the rebound from the induced hypoglycemia as criterion, it seems to prove more sensitive and specific than the oral glucose tolerance tests in the diagnosis of mild diabetes mellitus.

Curriculum vitae

Born on the 15th of December 1934 in Geneva, I lived in the United States of America from 1938 to 1946. After five years of schooling there, followed four years at the "Ecole Internationale" in Geneva, and four more years at the "Collège classique de Genève". With the "certificat de maturité, type B" I entered in 1954 the University of Geneva, where I passed the first propedeutical examination the following year. I then moved to the University of Zürich, where I passed the second propedeutical examination in the spring of 1957. In the following spring I entered the "Universidad Nacional Autónoma de Mexico" in Mexico City, but during the six months of my stay there I was ill most of the time. In November 1958 I started work as "research assistant" in biochemistry for Merck, Sharp and Dohme in Rahway, New Jersey, U.S.A., where I stayed until the autumn of 1959. At this date I returned to Zürich to complete my medical studies, which I ended successfully by passing the qualifying federal medical examination in November 1962. In January 1959 I married Miss Pat Hinxman from Banbury, England. A daughter, Heidi, was born to us in August 1962.

I wish to express my gratitude to Miss Annemarie Rosselet for her instruction and cheerful help in the biochemical work, and to Dr. Alois K⁶alin for help in the statistical analysis.

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Table 1

Comparative results of the blood sugar lowering effect after acute intravenous sulfonylurea administration

Authors	Substance (Method of blood sugar determination)	Quantity	Injected...	Number of subjects		Sampling time after injection - (Blood sugar values expressed in percent of fasting blood sugar)											
				N	D	15'		20'		30'		40'		45'		60'	
						N	D	N	D	N	D	N	D	N	D	N	D
Braverman et al. ^a (1956) (15)	tolbutamide	1 gm/10 cc	slowly	N 9 D 11						63	88					70	80
Pfeffer et al. (1957) (97)	carbutamide	1-2 gm/		N 18 D 30 ^{**}				72,0 ±8,5 ^s	96,6 ±4,5			54,6 ±9,9	91,7 ±5,0			60,2 ±12,5	85,8 ±7,0
de Meutter et al. ^a (1958) (82)	tolbutamide	40 mg/kg in 10% solution	within 3 minutes	N 5 D 7		62	96	48	90	39	85	43				70	77
Kaup (1958) (73)	tolbutamide (Hagedorn- Jensen)	2 gm/20 cc		N 12 D 10		81 ±2,7	97 ±1,3			60 ±3,6	94 ±1,3		61 ±2,2	90 ±2,3		72 ±1,8	87 ±2,4
Unger et al. (1958) (121)	tolbutamide (Sonogyi-Nel- son)	1 gm/20 cc	within 2 minutes	N 100 D 79				60,0 ±14,2	90,0 ±7,4	51,0 ±14,8	83,0 ±8,7	55,6 ±11,9	83,0 ±9,8			72 ±12,1	77,0 ±10,9
Zarewicz et al. (1959) (137)	tolbutamide (Follin-Wu)	1 gm/20 cc	within 2 minutes	N 25 D 26				64	89			60	74			74	70
Barretto et al. ^a (1959) (6)	tolbutamide (Sonogyi-Nel- son)	1 gm/10 cc	within 2 minutes	N D = 0		79				64			69			75	
Habitant (1961)	tolbutamide (Sonogyi-Nel- son)	1 gm/10 cc	within 2 minutes	N 28 D 26				69 ±11,5	87 ±7,2	53 ±9,1	77 ±5,6	54 ±9,1	72 ±10,6			70 ±8,8	67 ±11,8

^a - drawn from the curves published by the authors^s - estimate of standard deviation^{**} - a third had a fasting blood sugar of over 200 mg%

Table 2

Diagnostic criteria of the tolbutamide response test:A review

I) **Criteria:** The twenty and/or thirty minute blood sugar response values, expressed in percent of the initial fasting blood sugar concentration (%FBS).

	Diagnosed as	Normal	Probable Diabetic (latent)	Diabetic
1) Unger & Madison (121)				
at 20 minutes		< 80 %FBS		> 84 %FBS
<u>and</u> at 30 minutes		< 77 %FBS		
2) Barreto & Recant (6)				
at 20 minutes		< 77 %FBS		> 77 %FBS
3) Whitehouse & Lowrie (126)		< 80 %FBS		> 80 %FBS
at 30 minutes				
4) Kaplan (72)				
at 20 minutes		< 80 %FBS		> 84 %FBS
<u>and</u> at 30 minutes		< 77 %FBS		> 77 %FBS
5) Pote (100)				
at 20 minutes		< 75 %FBS	< 85 %FBS	> 77 %FBS
<u>and</u> at 30 minutes			> 77 %FBS	> 77 %FBS
6) Silver & Macher (106)				
at 30 minutes		< 50 %FBS	< 77 > 50 %FBS	> 77 %FBS

II) **Criteria:** The time of the minimal blood sugar concentration and the subsequent response to this hypoglycemia within the following 80 minutes.

1) Zarowitz & Eis (138) consider diabetes as excluded if the fall of blood sugar is rapid, reaches its minimum in 40 minutes, and is followed by a significant hypoglycemic responsiveness within the next 80 minutes.

III) **Criteria:** The different rates of glucose assimilation after intravenous dextrose injection without and with tolbutamide administration.

1) Bastenie, Conard et al.(4): The difference is much greater in non-diabetics than in diabetics.

INDIVIDUAL TOLUTANIDE RESPONSE

VALUES

The individual hypoglycaemic effect of a 1 g intravenous tolbutamide injection on twenty-six diabetic patients and on twenty-six nondiabetic controls.

A) 26 DIABETIC PATIENTS

A) 26 DIABETIC PATIENTS																					
case no.	age	sex	Blood sugar concentration in mg. percent						60 minus 30 minus		case no.	age	sex	Blood sugar concentration in mg. percent						60 minus 30 minus	
			fasting blood sugar				40 minutes after injection		30	40				fasting blood sugar				40 minutes after injection		30	40
			20	30	40	60	value	value	20	30				40	60	value	value	20	30	40	60
			FBS x_0				blood sugar expressed in percent of FBS		FBS x_0					blood sugar expressed in percent of FBS		FBS x_0				blood sugar expressed in percent of FBS	
				$\frac{x_{60}-x_{30}}{x_0 \cdot 10^{-2}}$		$\frac{x_{60}-x_{40}}{x_0 \cdot 10^{-2}}$						$\frac{x_{60}-x_{30}}{x_0 \cdot 10^{-2}}$		$\frac{x_{60}-x_{40}}{x_0 \cdot 10^{-2}}$							
56	42	F	82,5	56,0	47,0	36,5	36,5	-13,5	-0,0	6	81	F	95,0	75,5	67,0	65,0	62,5	-5,0	-2,5		
44	83	F	70,0	63,5	43,0	39,5	38,5	-6,5	-1,5	30	63	M	96,0	82,0	73,5	71,0	59,0	-15,0	-12,5		
58	81	M	76,0	64,0	50,0	53,0	47,5	-3,5	-7,0	40	81	F	99,0	92,0	76,5	72,0	65,5	-11,0	-6,5		
33	40	M	77,0	66,5	58,0	43,0	42,5	-20,0	-0,5	32	53	M	118,0	93,0	95,0	93,0	78,5	-14,0	-12,0		
17	47	F	79,0	69,0	65,0	54,5	44,5	-26,0	-12,5	49	53	M	122,0	110,0	102,5	100,0	89,0	-11,0	-0,0		
113	41	M	80,5	76,0	66,0	67,0	67,0	-1,0	-0,0	105	48	F	123,0	99,0	76,0	66,0	62,0	-11,0	-5,0		
111	55	M	89,0	71,5	69,5	65,0	61,0	-9,5	-4,5	22	67	M	125,0	112,0	106,5	105,5	101,5	-6,0	-3,6		
4	57	M	88,0	82,0	75,0	68,0	66,0	-10,0	-2,5	5	58	F	127,0	120,5	116,0	111,5	97,5	-14,5	-11,0		
29	72	M	90,0	71,0	65,5	59,0	58,0	-8,5	-1,0	24	56	F	130,0	115,0	106,5	100,5	89,0	-7,5	-1,0		
14	62	M	90,0	64,5	59,5	47,5	45,0	-13,0	-3,0	15	63	M	136,0	128,5	119,5	118,0	114,0	-6,0	-3,0		
117	49	M	90,5	70,5	50,0	42,0	37,0	-14,5	-5,5	48	72	M	152,0	144,0	142,5	140,0	129,5	-6,5	-7,0		
9	64	M	91,0	74,0	64,0	59,0	59,0	-5,5	-0,0	39	84	F	159,0	156,5	148,0	138,0	123,5	-15,0	-9,0		
101	24	M	95,0	71,0	62,5	52,5	52,0	-11,0	-1,5	1	25	M	167,0	153,0	152,0	137,0	131,0	-12,5	-4,0		

9) 28 NON - DIABETIC CONTROLS

a) 16 non-diabetic controls with minimum blood sugar concentration (medir) at 30 minutes after tolbutamide injection

b) 12 non-diabetic controls with
similar blood sugar concentration
(medir) at 40 minutes after
tolbutamide injection

[illegible]

Table 4
Investigations of the more promising criteria for the diagnosis of diabetes mellitus.

Criterion of differentiation	Y = mean of the group s _y = standard deviation	Group		Differentiation between	(0) $\bar{Y}_N - \bar{Y}_D = 0$		Graphical representation	
		Diabetic D	Non-diabetic subgroup N ₃₀		non-diabetic subgroup N ₄₀	diabetic group, D, and non-diabetic subgroup N ₃₀		diabetic group, D, and non-diabetic subgroup N ₄₀
Specificity S _D and specificity S _N when S _D = S _N To Solve:								
$S_N = \int_{-\infty}^{\infty} f(s_N ds_N) = S_D = \int_{-\infty}^{\infty} f(s_D ds_D)$								
A) Blood sugar values in %FBS								
a) at 20 minutes after the injection	$\bar{Y}$ s _y	86.6 7.16	75.0 5.62	D ⁺ & N ₃₀ D ⁺ & N ₄₀	.85 < s _{N30} = s _D < .90	.80 < s _{N40} = s _D < .85		
b) at 30 minutes after the injection	$\bar{Y}$ s _y	77.4 10.59	58.5 9.04	D ⁺⁺ & N ₃₀ D ⁺⁺ & N ₄₀	.90 < s _{N30} = s _D < .95	.80 < s _{N40} = s _D < .85		
B) Blood sugar fall in mg%								
a) at 20 minutes after the injection	$\bar{Y}$ s _y	13.3 6.88	21.2 6.07	D & N ₃₀ D & N ₄₀	.75 < s _{N30} = s _D < .80	.70 < s _{N40} = s _D < .75		
b) at 30 minutes after the injection	$\bar{Y}$ s _y	21.8 9.00	35.0 9.44	D & N ₃₀ D & N ₄₀	.85 < s _{N30} = s _D < .90	.75 < s _{N40} = s _D < .80		
c) at 40 minutes after the injection	$\bar{Y}$ s _y	27.7 10.26	42.8 9.77	D & N ₃₀ D & N ₄₀	.60 < s _{N30} = s _D < .65	.75 < s _{N40} = s _D < .80		
d) at 60 minutes after the injection	$\bar{Y}$ s _y	33.1 9.95	29.3 6.94	D & N ₃₀ D & N ₄₀	.75 < s _{N30} = s _D < .80	.60 < s _{N40} = s _D < .65		
C) Rebound from nadir								
1) Difference between the 60 minute values in mg% and								
a) the 30 minute values in mg%	$\bar{Y}$ s _y	-11.3 6.11	-5.6 3.95	D ⁺ & N ₃₀ D ⁺ & N ₄₀	.97.5 < s _{N30} = s _D < .98.75	.90 < s _{N40} = s _D < .95		
b) the 40 minute values in mg%	$\bar{Y}$ s _y	-5.4 4.81	-13.5 3.99	D ⁺ & N ₃₀ D ⁺ & N ₄₀	.95 < s _{N30} = s _D < .97.5	.95 < s _{N40} = s _D < .97.5		
2) Difference between the 60 minute values in %FBS and								
a) the 30 minute values in %FBS	$\bar{Y}$ s _y	-10.7 5.69	-6.0 4.35	D & N ₃₀ D & N ₄₀	.97.5 < s _{N30} = s _D < .98.75	.90 < s _{N40} = s _D < .95		
b) the 40 minute values in %FBS	$\bar{Y}$ s _y	-4.8 4.12	-16.0 4.42	D & N ₃₀ D & N ₄₀	.95 < s _{N30} = s _D < .97.5	.97.5 < s _{N40} = s _D < .98.75		

The prerequisites of normality and non-correlation to X (initial fasting blood sugar) of the population around its average for the use of the above formula (0) are probably (+) and very probably (++) not fulfilled

Underlined are the sensitivity specificity values of the best criterion of differentiation between diabetic and normal subjects.

Under the portion of the bell curve down is the percent of the population which is expected to be included within the boundaries of the criterion, it represents, when applied to the diabetics, the sensitivity, and when applied to the non-diabetics, the specificity of the criterion
($\bar{Y}_D$ or $N + 1 \cdot s_{yD}$ or M)

(N.B. Statistical symbols as in (56))

Table 5

Tentative criterion limits and corresponding sensitivity and specificity for the 60 minute values minus the 30 minute values and the 40 minute values expressed in percent of the fasting blood sugar concentration (%FBS).

Criterion limits and corresponding sensitivity and specificity

A) Sensitivity* = percent of diabetics correctly diagnosed as diabetics	60 minute %FBS value minus 30 minute %FBS value Criterion limits	Specificity for N ₃₀ * = percent of non-diabetics with nadir at 30 minutes correctly diagnosed as non-diabetics	B) Sensitivity* = percent of diabetics correctly diagnosed as diabetics	60 minute %FBS value minus 40 minute %FBS value Criterion limits	Specificity for N ₄₀ * = percent of non-diabetics with nadir at 40 minutes correctly diagnosed as non-diabetic
	+ 19,3	75,0 %		+ 12,8	75,0 %
	+ 17,5	80,0 %		+ 12,0	80,0 %
	+ 15,5	85,0 %		+ 11,0	85,0 %
	+ 12,2	90,0 %	99,95 %	+ 10,8	
99,95 %	+ 10,8			+ 9,7	90,0 %
	+ 8,7	95,0 %	99,75 %	+ 8,1	
99,75 %	+ 7,1			+ 7,7	95,0 %
99,5 %	+ 5,4		99,5 %	+ 6,9	97,5 %
	+ 4,9	97,5 %		+ 5,9	97,5 %
99,0 %	+ 3,6		99,0 %	+ 5,6	
98,75 %	+ 3,0		98,75 %	+ 5,2	
98,2 %	+ 2,4	98,2 %	98,2 %	+ 4,7	98,2 %
97,5 %	+ 1,3	98,75 %	97,5 %	+ 4,1	98,75 %
	+ 1,1			+ 3,8	
	+ 0,2	99,0 %		+ 3,5	99,0 %
95,0 %	- 0,9		95,0 %	+ 2,4	
90,0 %	- 3,2		90,0 %	+ 1,7	99,5 %
	- 3,3	99,5 %		0,7	
85,0 %	- 4,7			- 0,1	99,75 %
80,0 %	- 5,8	99,75 %	85,0 %	- 0,4	
75,0 %	- 6,6		80,0 %	- 1,2	
	- 6,5		75,0 %	- 1,8	
	- 14,5	99,95 %	50,0 %	- 4,4	99,95 %

* The sensitivity is the one sided tolerance limit of the diabetic population and the specificity is the one sided tolerance limit of the non-diabetics population for a given value of the criterion. The one sided tolerance limit is

$$\bar{Y} + \text{or} - s_Y ((1/n) + 1)^{1/2} \cdot t = \bar{Y} + \text{or} - s_Y \cdot t \quad (56,96)$$

Table 6

Results of 2 patients with liver disease

A) Abnormal Tolbutamide response tests of 2 patients with normal glucose tolerance curves, with no symptoms of diabetes, but with severe liver disease

case	Age	sex	FBS = 0	minutes after injection			
				20	30	40	60
a	75	M	90 = 100 %	81 = 90%	65=74%	56= 62 %	55=61 %
b	42	M	70 = 100 %	67 = 95%	55=78%	54= 77 %	48=68 %

B) Corresponding Staub-Traugott glucose tolerance curves of the patients with severe liver disease

case	FBS = 0'	15'	30'	45'	60'	75'	90'	120'	180'
a	90	123	150	140	103	122	149	93	77
b	79	113	125	117	93	114	114	101	81

20 gr. of glucose dissolved in 200 ml of water were ingested at 0 and 60 minutes.

Table 7

Influence of the initial fasting blood sugar concentration, sex and age on the time of the minimal blood sugar concentration (time of nadir) in non-diabetics.

a) Fasting blood sugar concentration (FBS) and time of blood sugar concentration minimum

	Minimum blood sugar at 30 minutes 40 minutes after injection		
Average FBS = $\bar{X}$	78,56	33,83	$P_{X_{40} - X_{30}} > 0.05$
Standard deviation = s_X	6,02	9,42	

b) Time of blood sugar concentration minimum compared with sex ($P_{\chi^2} > 0,25$)

Sex	Minimum blood sugar at 30 minutes 40 minutes after injection		Total
Male	8	9	17
Female	8	3	11
Total	16	12	28

c) Time of blood sugar concentration minimum compared with age ($P_{\chi^2} < 0.02$)

Age	Minimum blood sugar concentration at 30 minutes 40 minutes after injection		Total
Less than 50 years old	14	5	19
Older than 50	2	7	9
Total	16 N_{30}	12 N_{40}	28 $N_{30} + N_{40}$

Blood sugar concentration
in mg %

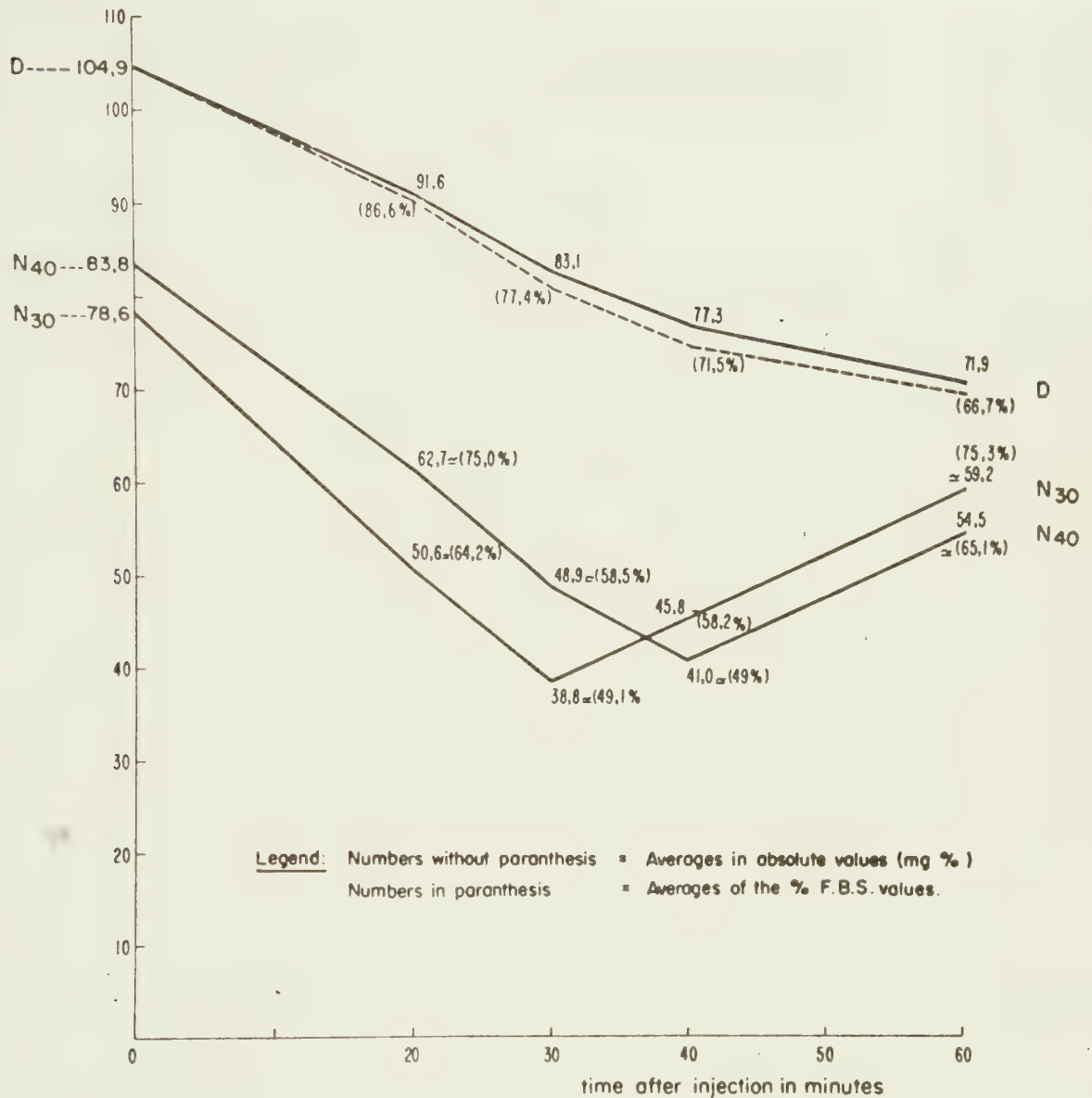


Figure 1

Averages of the diabetic patients (D) and the two non-diabetic control subgroups N30 (nadir at 30 minutes) and N40 (nadir at 40 minutes) after a tolbutamide intravenous injection

Diabetic patients =

Curve corresponding to the fitted curve of Figure 3 = ——— D

Non-diabetic controls

Subgroup with nadir at 30 minutes (N_{30}) = • Average of subgroup ——— N_{30}

Subgroup with nadir at 40 minutes (N_{40}) = x Average of subgroup ——— N_{40}

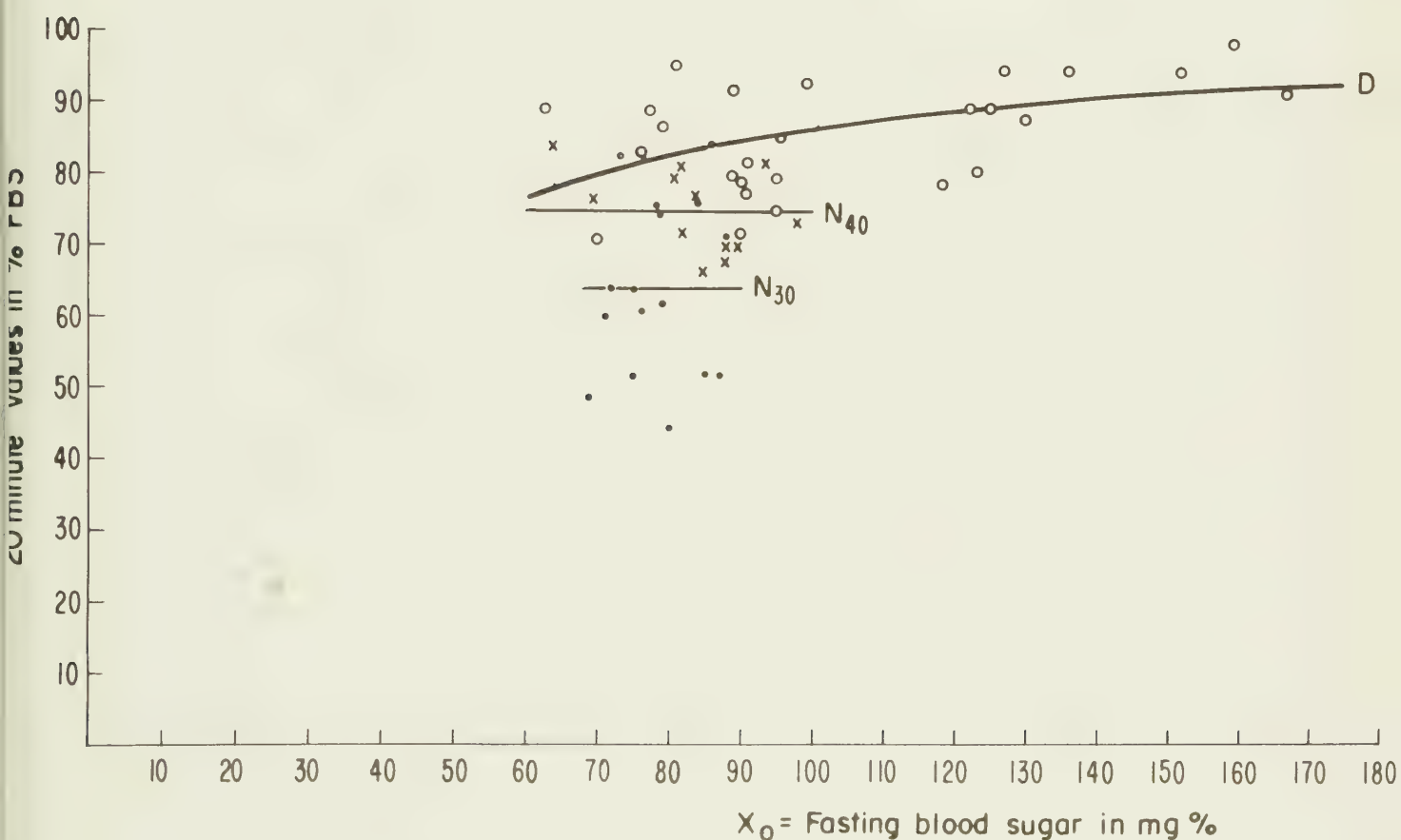


Figure 2*

The blood sugar concentration values in percent of the fasting blood sugar (% FBS) of the 20 minute sampling values, Y_{20} , depicted in Figure 2, plotted against the initial fasting blood sugar concentration (X).

Diabetic patients = o

Curve corresponding to the fitted curve of Figure 2 = ——— D

Non-diabetic controls

Subgroup with nadir at 30 minutes (N_{30}) = • Average of subgroup ——— N_{30}

Subgroup with nadir at 40 minutes (N_{40}) = x Average of subgroup ——— N_{40}

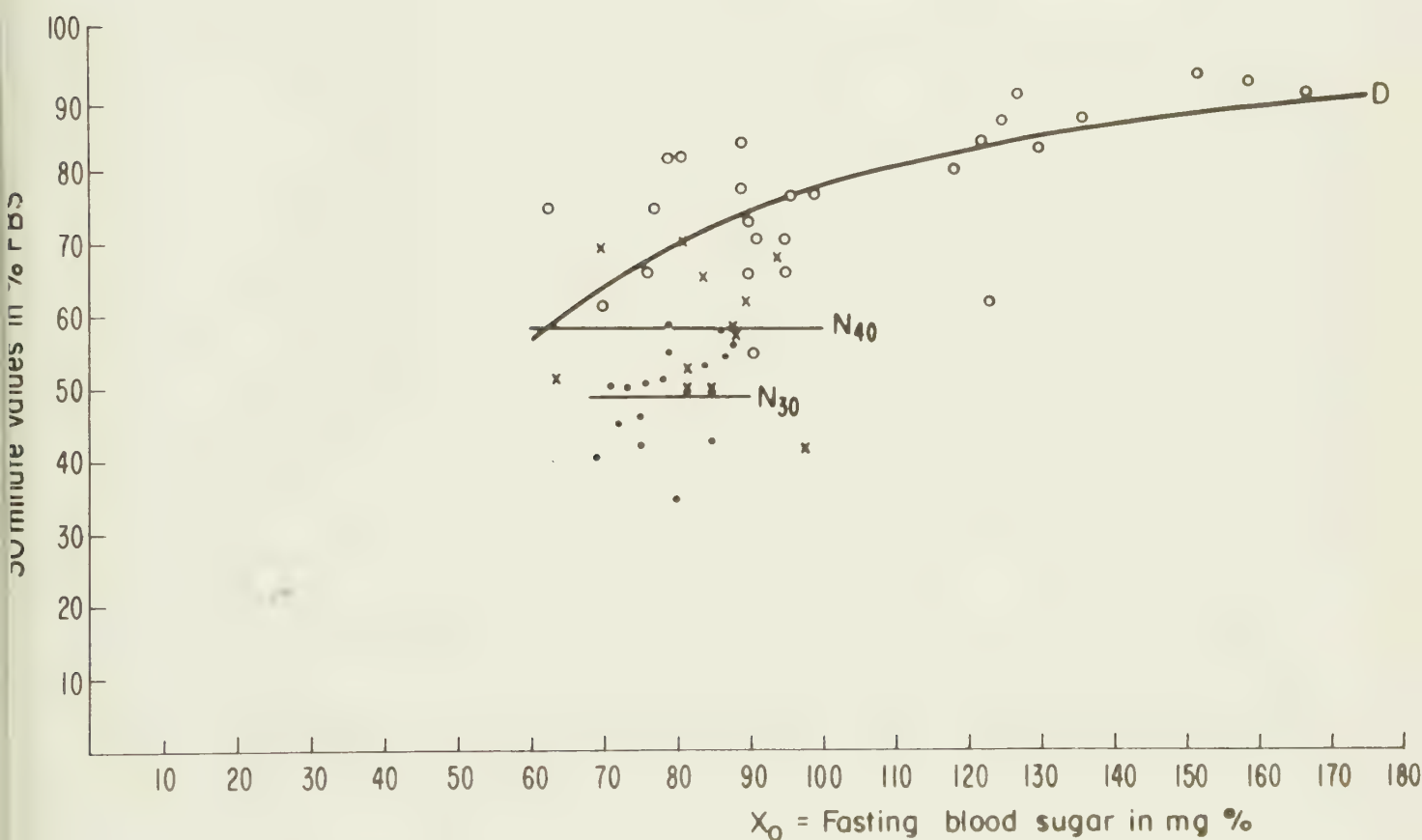
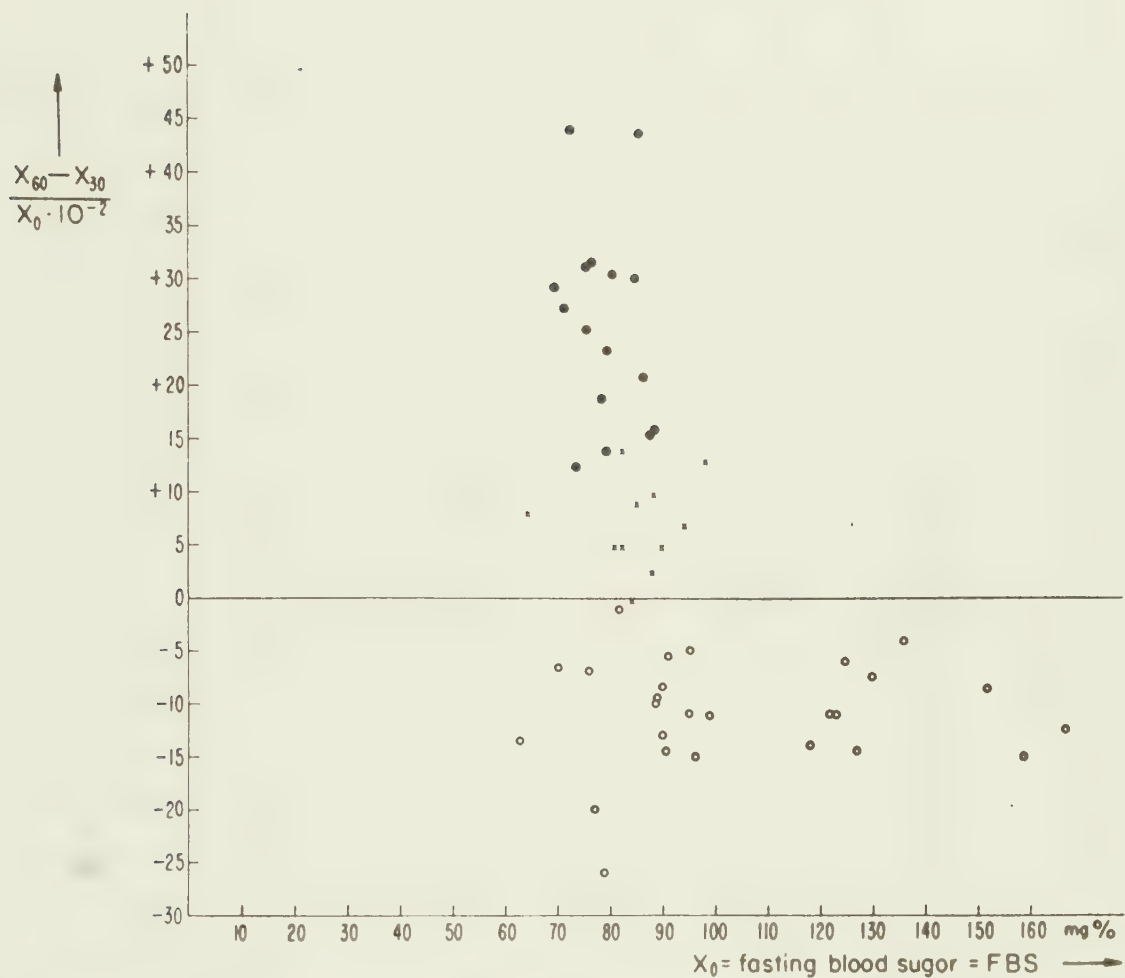


Figure 3*

The blood sugar concentration values in percent of the fasting blood sugar (% FBS) of the 30 minute sampling values Y_{30} , depicted in Figure 3, plotted against the initial fasting blood sugar concentration (X)



The differentiation between diabetics and non-diabetics using the sixty minute minus time of nadir values of the two non-diabetic subgroups.

Figure 4

The differentiation between diabetics (•) and non-diabetics of the subgroup $N_{30}(\circ)$; i.e. with time of nadir at 30 minutes. Criterion: The sixty minute % FBS values minus the thirty minute % FBS values.



The differentiation between diabetics and non-diabetics using the sixty minute minus time of nadir values of the two non-diabetic subgroups.

Figure 5

The differentiation between diabetics (x) and non-diabetics of the subgroup $N_{40}(X)$; i.e. with time of nadir at 40 minutes. Criterion: The sixty minute % FBS values minus the forty minute % FBS values.

